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Abstract

Title: Therapeutic composition for treating or preventing obesity and protecting against the development of its complications, and for treating complications that have developed

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The invention relates to a magistral galenic agent suitable for For^{} an effective pharmaceutical treatment of obesity. ~~the authors provide physicians with a magistral galenic agent, thus filling a therapeutic gap^{*}~~ The in this area. Their^{*} composition consists of several components, and contains, with regard to its quantitative make-up, 98.05% natural substances and only 1.95% pharmaceutical material.*

Owing to its lipolytic and appetite-suppressing action, the agent reduces body weight within a short time, and decreases the serum cholesterol, triglyceride and total fatty acid levels, an action which is more effective and lasts longer than that of any hitherto existing treatment. As a result, the composition is very effective in preventing arteriosclerosis and cardiovascular syndromes resulting therefrom, and in preventing diabetes or slowing the progress of existing disease. The results significantly improve the patients' psychological condition.

[Translator's note:] Handwritten material is illegible except for isolated words.

There is no illustration.

Lidia R. Fedina

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DEC. 30, 1998

Description and claims

Title of the invention

Therapeutic composition for treating or preventing obesity and protecting against the development of its complications, and for treating complications that have developed

(Trademark listing was requested under the name DESOBEX; during the examination period it was known under the nickname Syphex.)

Subject of the invention and its field of application

The invention relates to a multicomponent composition which has the effect of lowering the serum cholesterol, serum triglyceride and fatty acid levels, heightening metabolism, increasing lipolysis and decreasing lipogenesis, thereby producing significant weight loss.

Significance of the invention

According to the latest literature data, medicine still lacks an effective weight-reducing preparation. "Thus, in treating obesity, we remain without a therapeutic agent, so that for the time being all there is left is dieting and physical exercise" (*Gyógyszerek* 48, 2, 54-58 (1998))

At present, many people are firm believers in diet treatments — often administered in institutions — which people are very expensive (DM 4000-5000 per treatment) and are of questionable effectiveness; or they trust in "modified starvation" (*Dtaztebl.* 94, A-2250-2256, 1997). These treatments must be continued for a long time, with significant relapses and no results ("yo-yo" diet: *MOTESZ Mag.* 5, 32 (1998)). Other physicians, for lack of therapeutic alternatives, treat obese patients with large doses of single-component preparations which act on the central nervous system (*Gyak. Orv. Enc.*, 822, 1977). After having scored temporary successes, these agents have either disappeared from the market (Gracidine, Pondex, Desopimon) or their distribution has temporarily been suspended (Islipan), because the fenfluramine-phentermine combination can elicit valvulopathy and pulmonary hypertension (*JAMA* 278, 666-672, 1997; *New Engl. J. Med.* 335, 581-588, 1997; *Arch. Int. Med.* 144, 1143-1148, 1984; *New Engl. J. Med.* 337, 1772, 1997). High hopes were attached to orlistat, a synthetic derivative of a naturally occurring lipase inhibitor, but while tests with animals yielded favorable result, they failed in humans.

In cases of severe obesity and lipodystrophies, surgeons and plastic surgeons recommend surgery aiming at restricting food intake (reduction of stomach volume, ligation, etc.), reduction of absorption (enteroanastomosis), elimination of accumulated fat tissue (liposuction series) and/or removal of excess skin and fat (dermolipectomy). But the majority of patients with the most severe disease are, because of their general condition, not suitable subjects for physical stress or surgery (authors' statement based on *Magyar-Petrányi*, Med. Kiad. 1656, 1974).

In this imperfect therapeutic system of debatable success, the present invention could play a significant role in the prevention and effective treatment of obesity, and protection against all complications.

To understand the essence of the invention, it is necessary to discuss the up-to-date etiology and prevalence of the disease and its severe complications.

Obesity is an excessive increase of the body's fat content. The calorie intake exceeds the loss of calories, and the difference appears in the form of fat deposition. Obesity is arbitrarily defined as a condition where the body weight is 20% above the value given in the height/weight tables.

Several known formulas are in use (Broca, Bornhardt, etc.). In recent times the body mass index (BMI) is used, which is equal to the body weight in kg divided by the body surface area in m² (*MSD Melania* 984, 1994).

Classification: Mild	20-40% excess weight
Moderate	40-100% excess weight
Severe	more than 100% excess weight.

It is incorrect to distinguish between fat and obese people. It is more accurate if a healthy (symptom-free) fat person is also considered sick, because it is easier to influence obesity at the time it begins and severe complications have not yet developed *A Gyak. Orv. Encik.* [The Practising Physician's Encyclopedia], Medicina, 819, 1977).

The incidence of obesity in the U.S. is 24% for men and 27% for women. The incidence between the ages of 20 and 50 increases to twice this figure, and in women living under poor social conditions it is twice as high as in higher social strata. In black women it attains 60% (*MSD Melania* 981 (1994)). In developed countries and in those of average development, obesity is

present in nearly 70% of the adult population, and this situation is typical of our country as well. For this multitude of sick people to diet and exercise only is an illusory idea.

The exact cause of obesity is unknown. In the past, it was considered to represent only a metabolic disorder, which was attributed to excessive food intake. According to the latest scientific opinion, in addition to exogenous (nutritional) excess weight, endogenous factors (genetic, hormonal, neural and metabolic disorders) also play a significant role in the pathogenesis of obesity. The two principal factors are closely related and overlap. As a result of excess food intake, the metabolic equilibrium is upset, internal disorder develops, and hyperinsulinism occurs, which causes an aggressive hunger sensation (Moron, 1978). This is accompanied by psychosomatic problems, and a stress/overweight / stress situation is brought about which is a self-engendered vicious circle. Stress leads to excess weight, and excess weight causes stress. At least seven factors contribute to its development and form a certain system. These are: genetic factors, social factors, endocrine and metabolic factors, psychological factors (bulimia, nocturnal eating syndrome), developmental growth factors (hypertrophic and hyperplasmic obesity and combinations thereof), physical inactivity and cerebral damage (injury of the ventromedial hypothalamic nucleus which causes hyperphagia and obesity).

Obesity is involved in the etiology of several severe diseases (no mention will be made of the forms of obesity associated with endocrine diseases). The direct connection between diabetes, cardiovascular diseases, arteriosclerosis and obesity are well known. Obesity also has an effect on the status of the respiratory system, gastrointestinal tract, kidneys, genitals, nervous system, skin and organs of locomotion.

The importance of obesity is supported by the following data:

After several decades of practicing medicine, we can state that the mortality of obese individuals increases parallelly to their body weight. Hence these patients find it difficult or impossible to obtain life insurance. Being overweight by more than 25%, increases mortality by 75%. Compared with the mortality of diabetics of normal weight, the mortality of severely obese diabetics is 400%. Surgical mortality is 300%. Obese persons suffer accidents more frequently, and injury to the organs of locomotion is more common.

Principal object of the invention

Preparation of a human magistral galenic agent, which, without major side effects, and combined with a normal lifestyle, effectively reduces body weight, lowers serum cholesterol, triglyceride and total fat levels, and prevents or reverses the consequences and complications of obesity. Our goal is to produce a harmonic, natural, secretory composition by utilizing lyophilized organs, natural active plant substances and synthetic components, in other words to offer a pharmacodynamic and by no means hormonal substitutive therapy. The multifactor combination results in a potentiated mechanism of action, which makes it possible to reduce the dosage of the individual factors.

The characteristic features of the invention are as follows:

- The composition is contained in a gelatin capsule which can be orally administered;
- It contains existing, tested substances, each of which has been used individually;
- It is a multicomponent composition whose components are present in small quantities;
- It is mainly an organotherapeutic preparation which has a pharmacodynamic activity;
- It contains mainly natural substances (98.05%) and only 1.95% of its contents is a pharmaceutical material;
- It contains no preservative;
- As a magistral galenic product, it may also be prepared individually;
- It can be manufactured on an industrial scale.

The principal components of the composition according to the invention are:

1. Glandulae thyreoideae sicc. [dried thyroid gland] 35-45 mg

Its function is to enhance the basic burn-up of calories, increase metabolism, intensify lipolysis and decrease lipogenesis. Improvement of defective thyroid gland function. (According to statistical surveys, 25% of the general population suffer from hypothyroidism (Rucz, 1998). It releases a significant amount of energy. It prevents cardiac infarction without making the patients adhere to a special diet or change their lifestyle or give up smoking. It exerts this action without active exercise. It is a known fact that the substance significantly increases the life expectancy of patients who have suffered an infarction. This may be attributed mainly to improved coronary circulation (Russe, *Abstr. of the 32nd Sci. Sess.*). During treatment, the blood pressure decreases, as does the sensation of fatigue. In patients treated with thyroid, protein-

bound iodine remains constant in a statistically significant manner, while the serum cholesterol level and β -lipoprotein fraction decrease (Moses et al., *Abstr. of the 31st Sci. Sess.*, 761). Broda and Barnes have investigated 725 male and 844 female patients who had undergone thyroid therapy for 18 years, and found that coronary disease developed in only 4 cases, instead of the 72 which may have been expected on the basis of the size of the patient population. Moreover, these 4 cases consisted of patients over 55 years of age who belonged to a high-risk group. According to the aforementioned authors it is obvious that cardiac infarcts may be prevented in 94% of the cases by thyroid treatment alone, without requiring any change in the patients' lifestyle.

In Hungary, this component was known under the names thyreoideum siccum and Thyreoidea drg., but at the present time the best quality of this substance can only be obtained in Western Europe in a freeze-dried and sterilized form, controlled and tested according to EU standards.

2. TA3 (triiodothyronine acetate) 0.4-0.8 mg

Its main effect consists in burning up calories by activating triglyceride phosphate dehydrogenase (Galton, Bray, *Clin. Endocr.* 27, 1573-1580, 1967). As a result of its action, metabolism and lipolysis are significantly increased. Oxygen utilization is enhanced, and the respiratory quotient is higher. It has a specific lipolytic activity. It inhibits the conversion of carbohydrates into fat, and decreases the fat content of the body (Bray, *Clin. Invest.* 48, 1413-1422, 1969; Arnal, Bourquin, *Sem. Hop.* 52, 99-101, 1976).

It stimulates the hypothalamic sympathetic centers, and it is mainly through this action that it increases the metabolism. It directly increases cell oxidation. Treatment with the alpha derivative is well tolerated by patients. It increases basal metabolism as soon as after 12-24 hours, and develops its maximal effect within 2-3 days. It lowers the serum cholesterol level by 20-30%.

3. Pancreatin powder 100-300 mg

In obese patients the endocrine and exocrine functions of the pancreas is exhausted, hence obesity may be considered a condition preceding diabetes, or in the decisive majority of cases it leads to diabetes. The sterilized pancreatin powder of bovine origin prepared by freeze-drying, (and tested according to EU standards) retains its amylase, lipase and protease activities, while it has no significant insulin effect when orally administered. In lyophilized pancreatin powder the proteolytic enzymes remain in an inactive form (chymogen). They initiate digestion as early as in the stomach, assisting the exhausted pancreas. Contrary to the most recent conceptions

(administration of orlistat, a lipase inhibitor for inhibiting fat absorption, for example) we believe that the breakdown of fats is important, since without it vitamins cannot be absorbed either, the “tired stomach” syndrome becomes more severe, and instead of digestion, fermentation becomes more primary, while the feeling of discomfort in obese patients is intensified.

In Hungary, pancreatin used to be obtained by aqueous extraction, and marketed as a yellowish gray powder, mainly for the treatment of chronic catarrhal pancreatogenic disease in children, achylia and dyspepsia. Lukullin, Dipancrin and Cotazym forte continue to be known products (*Gyógyszerrendelés*, 376-379, 1979). However, aqueous extraction no longer meets modern production requirements. Considered as an up-to-date preparation is Pankreolat coated tablets, produced from porcine pancreas (*Vademecum*, 985, 1996).

4. Titrex hyoscyamus 7-12 mg (0.3% alkaloid)

Alkaloid extracted from the plant. It is a vegetative agent, chemically related to atropine. It paralyzes the cholinergic nerve endings. Because of its parasympathetic action it has a stronger effect in reducing salivary and gastric juice secretion than atropine, but its cardiac vagal effect is weaker. At first, it rather slows the pulse. In contrast to atropine it does not stimulate the central nervous system. It stops motor excitation, thus preventing the unpleasant side effects of thyroid. It decreases vegetative lability, and inhibits salivary and gastric juice secretion, thus causing dryness of the mouth; but it also attenuates hunger sensations and complaints of hyperacidity.

5. Titrex passiflorae [passion flower] 20-40 mg (6% alkaloid)

Parasympatholytic agent extracted from a hyoscyamus-like plant. Its effect is weaker. It has almost no effect on the central nervous system, but its peripheral activity is similar. It reduces salivary and gastric juice secretion, causes dryness of the mouth, attenuates the sensation of hunger and complaints of hyperacidity. Vegetative agent, assists the effect of hyoscyamus and decreases the motility-enhancing effect of thyroid.

6. Extractum valerianae e rad. aquos sicc. [aqueous extract from dried Valerian root], 30-55 mg
Admixed to the composition in small doses (in the present case the dose is that given to infants), it has a mild tranquilizing effect. It does not cause drowsiness or CNS symptoms, and does not prolong the duration of the reaction. It compensates possible restlessness resulting from the released energy or from the action of thyroid.

7. Gonads

- For female patients: Ovary powder 70-110 mg (92.6% protein)

It is an accepted fact that the gonads participate in fat metabolism. With obesity, sex characteristics are relegated to the background and their function decreases. This is indicated also by the fact reported in the literature that, even in the case of moderate obesity, menstruation ceases, or its orderly schedule undergoes changes (*Magyar-Petrányi*, Med. 1662, 1974; *MSD, Mel.*, 983, (1994). Complaints resembling menopause become more pronounced. Diminished ovarian function also plays a significant role in the development of osteoporosis. Instead of administering hormones, we stimulate the body toward adopting a "youthful disposition" by admixing natural ovarian powder to the composition.

- Male patients: Testis siccum [dried testis] 5-15 mg (87% protein)

The testes also participate in lipolysis. With obesity, male sex characteristics decrease. The shape of the body becomes more feminine. The libido decreases, and impotence may develop (*Magyar-Petrányi*, Med. 1662, 1974). When lyophilized testis powder is administered orally, the body makes use of the missing constituents as a stimulant, while it disposes of unnecessary substances.

8. Cofactors acting on the hypothalamus (it is sufficient to use only one of the substances listed below)

The effect of the natural extracts is assisted and enhanced by the administration of small doses of a cofactor which acts on the hypothalamic hunger center. The object is not weight loss but appetite suppression.

- Fenfluramine hydrochloride 2-3 mg

The literature on this substance extends to many volumes. Its advantages in the treatment of obesity have surpassed its drawbacks or alleged drawbacks by several orders of magnitude. However, we, ourselves have suspended its use (despite the fact that we used it in a dose of a lower order of magnitude than the recommended drug dose) until it is clearly demonstrated that the pulmonary hypertension and heart-valve changes encountered in the U.S. are definitely caused by administration of the drug, instead of being merely the consequence of obesity.

- Clobenzorex hydrochloride 4-8.4 mg

This is an amphetamine derivative. It eliminates the harmful effects of amphetamine, while retaining the appetite-suppressing activity, without causing habituation. In France it is the basic component of the weight-reducing agent known under the official name of Dinintel. The therapeutic drug doses are 5 to 10 times higher than the dose recommended by us. Apart from its appetite-suppressing effect, it lowers the total lipid, cholesterol and lipid phosphoric acid level of the blood. It also has a moderate central, psychostimulating effect. In the dose recommended by us it does not cause hypermotility, tachycardia or sleep disorder.

- Serotonin reuptake inhibitor: Fevarin 30-50 mg

Fluvoxamine, a new type of serotonin reuptake inhibitor, which has only a minimal effect on adrenergic processes (*Vademecum*, 484, 1996). It improves the patient's mood, hence it is an excellent antidepressant. For our purposes its important effect is to induce a loss of appetite, which we can effectively utilize in a composition prepared for treating obesity. Its use does not endanger individuals working in high places, or drivers of motor vehicles.

Steps in the preparation of the pharmaceutical composition; formulation

For therapeutic use, the composition according to the invention is expediently converted into a pharmaceutical composition by blending it with auxiliary substances generally used in drug preparation and forming it into one of the usual drug [dosage] forms. The expression "usual drug [dosage] form" is understood to mean oral preparations; thus for example, capsules, which in a particular case are produced under sterile conditions in batches of up to 200 capsules, in order to rule out quantitative scatter. According to our recipe, the individual components are measured out in increasing quantitative order, under thorough mixing. The components are in a very fine pulverulent form, hence are easy to mix together. Taking into consideration the caliber of the capsules (No. 2 gelatin capsules) and the conditions of absorption, the capsule contents are supplemented with certain auxiliary materials used in pharmaceutical preparations. The powder mixture is screened five times to a No. 5 sieve fineness, an operation which also promotes homogeneity. Using a semi-automatic machine (Weber), the half capsules are placed on its lower plate and filled with the previously prepared mixture. The upper capsule part is automatically pressed by the machine on the filled capsule. Wearing rubber gloves, handlers make up the product into packages containing two-week portions.

Advantages of the invention

1. Contrary to the official edict, there is potential for an effective, humane therapy for obesity;
2. The composition of the invention is nontoxic even when administered in large doses (see appended study of the POTE [Medical University of Pécs] Pharmaceutical Institute, where research was carried out on the drug known under the nickname Syphex);
3. A two-week treatment results in an average weight loss of 4 to 6 kg;
4. Lipogenesis is reduced, and lipolysis is increased;
5. Appetite is decreased and the feeling of satiety is increased;
6. Hypertension is improved;
7. Diabetic condition is improved, the need for antidiabetic drugs is reduced, the blood-sugar level is stabilized;
8. Serum total-lipid, triglyceride and cholesterol levels are lowered;
9. The composition does not significantly stimulate the central nervous system, and does not cause insomnia;
10. It is not habit-forming;
11. Menopausal symptoms are improved; osteoporosis could be delayed;
12. The sclerotizing process is stopped;
13. The patients' psychological state is significantly improved;
14. On the basis of several hundred computerized fat investigations carried out in Germany, it can be unequivocally proved that the weight loss arises as a result of reduction of the fat mass, while the fat-free mass does not decrease, or does so only to a minimal extent.

Drawbacks of the invention

1. Product consists of several components;
2. It is expensive to prepare;
3. Gaining domestic recognition is difficult and slow;
4. It has well-specified contraindications (pregnancy, liver disease, chronic alcoholism, paroxysmal tachycardia, malignant hypertension, prepubertal period);
5. Initiation of treatment requires medical examination.

Claims

1. Therapeutic composition useful in preventing moderate and severe obesity and its complications, said composition exerting its weight-reducing effect by a breakdown of fats and prevention of the latter's assimilation.
2. Composition according to Claim 1, characterized in that, apart from weight reduction, it lowers the serum cholesterol, triglyceride and total fatty acid levels, thereby preventing cardiovascular and atherosclerotic diseases and the complications thereof.
3. Composition according to Claim 1, characterized in that, by decreasing the fat mass, it prevents or improves the diabetic condition, and stabilizes the blood sugar level.
4. Composition according to Claim 1, characterized in that as a result of the weight reduction achieved by appetite suppression and fat breakdown, it improves the patient's psychological state.

10720/1998. 12. 27.

Kaposvár, Dec. 27, 1998

[Signed] Dr. István Lelkes

[Signed] Dr. István Seffer

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